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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/948,149	10/09/97	[illegible]	

EXAMINER	
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ART UNIT	PAPER NUMBER
1641	7

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DATE MAILED: 09/28/98

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 30 JUL 1998

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), ~~or thirty days~~, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-41 is/are pending in the application.
Of the above, claim(s) 1-27, 41 is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 28-40 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☒ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

DETAILED ACTION

1. Applicants' Response to Restriction, received 30July1998, paper#6, is acknowledged. Applicants elect, without traverse, Invention V, claims 28-40, drawn to a method for inducing cell death. Claims 1-27 and 41 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to a non-elected invention.

2. Currently, claims 28-40 are under consideration.

Drawings

3. This application has been filed with drawings which are acceptable for examination purposes only. The drawings are objected to for the reasons set forth on the attached form PTO-948.

Specification

4. The disclosure is objected to because of the following informalities:

a) throughout the specification, monoclonal antibodies designated 7C2, 7F3, and 4D5 are usually labeled as being anti-ErbB2 antibodies. However, on some occasions, the 7C2, 7F3, and 4D5 are labeled as being anti-HER2 antibodies. Clarification is required concerning whether anti-HER2 and anti-ErbB2 denote the same meaning. If there is a difference, the difference should be noted. If there is no difference, then for the sake of consistency, all designations should be anti-ErbB2.

b) page 51, lines 16-17, the American Type Culture Collection address cited in the specification is no longer correct. Effective 23March1998, the correct address is 10801 University Boulevard, Manassas, VA 20110-2209,

Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. Claim 28-40 are rejected under 35 U.S.C. 112, second paragraph, as being dependent to a nonelected claim.

Claim 28-39 are dependent to claim 1 which is a nonelected claim. Incorporation of the pertinent criticalities of claim 1 into claim 28 will obviate the rejection.

Claim 40 is dependent to claim 9 which is a nonelected claim. Incorporation of the pertinent criticalities of claim 9 into claim 40 will obviate the rejection.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

8. Claims 28-31, 37-38 and 40 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Shepard et al (*J. Clin. Immunol.*, 11(3):117-127, 1991).

The instant claims utilize the open language "comprising" in delineating the methods steps. Such language encompasses induction of apoptosis which is taught in the instant specification as one of the mechanisms by which the claimed antibodies induce cell death, but the scope of the claim is not restricted only to apoptosis, nor is the language restricted as to the use of other reagents, such as complement, phagocytic cells, cytotoxic drugs, or growth inhibitory agents, in addition to the antibodies.

Shepard et al teach a monoclonal anti-HER2 antibody (4D5) which: a) inhibits the growth of SKBR3 breast tumor cells in cell culture by 66% (Abstract; Table II); b) enhances the sensitivity of SKBR3 cells to cisplatin (Figure 5); and c) enhances the sensitivity of SKBR3 cells

to TNFα (Figure 4). Shepard et al also teach monoclonal anti-HER2 antibodies 7C2 and 7F3 which bind to Domain 1 of ErbB2 (Figure 2; page 119, section **Derivation of muMab 4D5**) and which inhibit SKBR3 proliferation by 21% and 38% respectively (Table II).

9. Claims 28-31, 37-38 and 40 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Lewis et al (*Cancer Immunol. Immunother.*, 37:255-263, 1993).

The instant claims utilize the open language "comprising" in delineating the methods steps. Such language encompasses induction of apoptosis which is taught in the instant specification as one of the mechanisms by which the claimed antibodies induce cell death, but the scope of the claim is not restricted only to apoptosis, nor is the language restricted as to the use of other reagents, such as complement, phagocytic cells, cytotoxic drugs, or growth inhibitory agents, in addition to the antibodies.

Lewis et al teach monoclonal anti-HER2 monoclonal antibodies, e.g., 4D5, 7C2, and 7F3, which inhibit human tumor cells such as SKBR3 (Table 2) and mediate antibody-dependent cellular cytotoxicity (Figure 4).

10. Claims 32-36, and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable Shepard et al (*J. Clin. Immunol.*, 11(3):117-127, 1991), or Lewis et al (*Cancer Immunol. Immunother.*, 37:255-263, 1993), in view of Fendly et al (*Cancer Research*, 50:1550-1558, 1990), Deshane et al (*J. Invest. Med.*, 43(Suppl 2):328A, 1995), and further in view of Senter et al (U.S. Pat. No. 4,975,278).

The instant claims utilize the open language "comprising" in delineating the methods steps. Such language encompasses induction of apoptosis which is taught in the instant specification as one of the mechanisms by which the claimed antibodies induce cell death, but the scope of the claim is not restricted only to apoptosis, nor is the language restricted as to the use of other reagents, such as complement, phagocytic cells, cytotoxic drugs, or growth inhibitory agents, in addition to the antibodies.

Shepard et al teach a monoclonal anti-HER2 antibody (4D5) which: a) inhibits the growth of SKBR3 breast tumor cells in cell culture by 66% (Abstract; Table II); b) enhances the sensitivity of SKBR3 cells to cisplatin (Figure 5); and c) enhances the sensitivity of SKBR3 cells to TNFα (Figure 4). Shepard et al also teach monoclonal anti-HER2 antibodies 7C2 and 7F3 which bind to Domain 1 of ErbB2 (Figure 2; page 119, section **Derivation of muMab 4D5**) and which inhibit SKBR3 proliferation by 21% and 38% respectively (Table II).

Lewis et al also teach monoclonal anti-HER2 monoclonal antibodies, e.g., 4D5, 7C2, and 7F3, which inhibit human tumor cells (Table 2) and mediate antibody-dependent cellular cytotoxicity (Figure 4).

Fendly et al teach the production and characterization of the monoclonal anti-HER2 antibodies utilized by Shepard et al and Lewis et al (Abstract; page 1550-1552, section **Materials and Methods**).

Deshane et al teach that intracellular antibody knockout of the ErbB2 oncoprotein achieves targeted eradication of tumor targets by induction of apoptosis.

Senter et al teach a method for delivery of cytotoxic drugs to tumor cells by using a tumor specific antibody/enzyme conjugate that binds to the tumor cells, and upon additional administration of a prodrug, the enzme converts the prodrug to an active cytoxic drug (Abstract; Figure 1; column 4, line 5 to column 5, line 4).

Thus, it would have been obvious at the time the invention was made to a person having ordinary skill in the art to use the monoclonal anti-HER2 monoclonal antibodies, such as 4D5, 7C2, and 7F3, as taught by Shepard et al, Lewis et al, and Fendly et al to induce cell death in cells overexpressing ErbB2 receptor by a variety of methods, one of which is apoptosis. Likewise, it would have been obvious at the time the invention was made to a person having ordinary skill in the art to enhance the efficacy of the monoclonal antibodies by using the reagents and techniques taught by Senter et al, or by using in concert with the monoclonal antibody treatment, radiation treatments as widely used in the treatment of tumors.

Conclusion

11. The following prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Kita et al (*Biochem. Biophysic. Res. Commun.*,226:59-69, 1996), ErbB receptor activation, cell morphology changes, and apoptosis induced by anti-Her2 monoclonal antibodies.

Thorpe et al (*U.S. Pat. No.* 5,776,427), Methods for targeting the vasculature of solid tumors. 7-7-98.

Arakawa et al (*U.S. Pat. No. 5,783,186*), Antibody-induced apoptosis. 7-21-98

12. No claims are allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rodney P. Swartz, Ph.D., whose telephone number is (703) 308-4244. The examiner can normally be reached on Monday through Friday from 6:30 AM to 4:00 PM EST.

If attempts to reach the Examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached on (703)308-4027. The facsimile telephone number for the Art Unit Group is (703)308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the group receptionist whose telephone number is (703)308-0196.

Rodney P. Swartz, Ph.D.

September 25, 1998

JAMES C. HOUSEL 9/26/98
SUPERVISORY PATENT EXAMINER